Trastuzumab and its radioimmunoconjugates in treatment of cancer

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Main text

Introduction

Monoclonal antibodies are new type of targeted anticancer therapy, which achieve specificity, selectivity and localization in tumor cells. There are many naked antibodies and immunoconjugates commercially approved for different types of cancer (Mehren et al., 2003). In order to improve specificity and selectivity of cytotoxic drugs and toxins, monoclonal antibodies are used for formulation of immunoconjugates. Many efforts are done to develop stable immunoconjugates of trastuzumab with various drugs, toxins and radioisotopes to improve the general conditions of the patients (Sharkey and Goldenberg, 2006). The aim of this paper is to focus on current achievements in the formulation of radioimmunoconjugates of HER2-targeting trastuzumab.

Trastuzumab is a humanized IgG1 monoclonal antibody active against HER2 positive breast cancer. Originates from murine antibody 4D5 that is potent inhibitor of HER2 positive cancer cells. Subsequently, it was chosen for further clinical development in order to reduce the probability of generation of HAMA (human anti-murine antibody) (Harries and Smith, 2002). Carter et al. (1992) cloned hypervariable regions from 4D5 in plasmids which encode formation of constant regions from human IgG1 antibody and generated a vector that encode formation of chimeric antibody which is

additionally humanized. The new humanized 4D5 has higher affinity for the HER2/neu antigen and reduced immunogenicity. Trastuzumab is acting by binding to the IV subdomain of the HER2 receptor and Fc region of the antibody support ADCC (antibody-dependent cellular cytotoxicity) (Gennari et al., 2004).

Radioimmunoconjugates for imaging and therapy

Because of the easy detection, radioimmunoconjugates can be used for body imaging at a molecular level using sensitive imager like γ camera, computed tomography and positron emission tomography (PET) (Goldenberg, 1997). Significant radiopharmaceuticals based on peptide and antibody for diagnostic and therapeutic purpose use different radioisotopes (99mTc/188Re, 67Ga, 177Lu, 90Y, 131I) (Kassis, 2008). In order to obtain successful labeling, previously conjugation with a bifunctional chelators (DOTA - 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid; DTPA - diethylenetriamine pentaacetic acid; TCMC - (1,4,7,10-tetra-(2-carbamoyl methyl)-cyclododecane; HYNIC - succinimidyl-6-hydrazino-nicotinamide; 1B4M-DTPA - 2-(4-isothiocyanatobenzyl)-6-methyl-diethylene-triaminepentaacetic acid) is required. These chelators allow binding to the antibody on the one side, and coordinative binding of radioisotopes on the other side (Kang et al., 2012).

Immunoconjugates of trastuzumab for PET imaging

In recent years there have been significant achievements in development of stable immunoconjugates of trastuzumab for PET imaging of HER2 positive lesions (Hooge et al., 2004). Chen et al. (2008) used 99mTc in order to create a stable conjugate, ^{99m}Tc-NYCIN-trastuzumab, useful for identification of HER2 positive metastasis. Tamura et al. (2010) have shown the possibility of identification of HER2 positive lesions in patients with primary metastatic breast cancer with ^{64}Ga-DOTA-trastuzumab. Three years later, Alitezapour et al. (2013) were able to formulate similar conjugate with another gamma emitter ^{67}Ga-DOTA-trastuzumab for the same purpose. Investigations of Palm et al. (2003) for pharmacokinetics of trastuzumab labeled with pure β emitters ^{86}Y and ^{90}Y in mice with ovarian cancer, were shown a selective uptake of the conjugate by the tumor cells and minimal localization in healthy organs. *In vitro* and *in vivo* investigations in mice with breast tumor show that ^{177}Lu-DOTA-trastuzumab can be new promising drug in treatment of human breast cancer (Rasaneh et al., 2012). Tan et al. (2012) have shown that ^{212}Pb-TCMC-trastuzumab has a significant therapeutic effect in HER2/neu positive prostate cancer. Borchardt et al. (2003) have tested therapeutic effects of alpha emitters ^{227}Th-DOTA-p-benzyl-trastuzumab and ^{225}Ac-trastuzumab in mice with HER2 positive breast and ovarian cancer. Studies have shown rapid internalization and cytotoxicity in cancer cells which leads to a extend survival and low toxicity.

Our examinations will be focused on synthesis and evaluation of the immunoconjugates of trastuzumab with bifunctional chelators (DOTA, DTPA and 1B4M-DTPA) with already used method for freeze dried kit formulation of rituximab-conjugates. The most stable immunoconjugate will be labeled with gamma emitter Ga-68 for further *in vitro* characterization and *in vivo* biodistribution. The simplicity of Ga-68 labeling will increase the access of radioimmunoconjugates in hospitals for PET imaging of HER2 positive metastasis.

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